PRODUCT MONOGRAPH

Amiloride Hydrochloride Tablets, USP

(amiloride hydrochloride tablets, USP)

Tablets 5 mg

Antikaliuretic Agent with Diuretic Properties

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THERAPEUTIC CLASSIFICATION

Antikaliuretic Agent with Diuretic Properties

ACTION AND CLINICAL PHARMACOLOGY

Amiloride Hydrochloride Tablets, USP is an antikaliuretic drug with mild natriuretic diuretic and antihypertensive activity. These activities may be additive to the effects of thiazides or other saluretic-diuretic agents. The principal use of Amiloride Hydrochloride Tablets, USP is to conserve potassium in selected patients receiving kaliuretic-diuretic agents. Amiloride Hydrochloride Tablets, USP interferes with the mechanism involved in the exchange of sodium for potassium in the distal convoluted tubule and collecting duct of the nephron. An increase in sodium and a decrease in potassium and hydrogen ion excretion are induced in the presence or absence of aldosterone, thereby suggesting a direct tubular action of the drug. Chloride excretion may remain unchanged or increase slowly with continued therapy.

Amiloride Hydrochloride Tablets, USP when administered with hydrochlorothiazide has been shown to result in less excretion of magnesium than thiazide or loop diuretics used alone.

Approximately 50% of an oral dose is absorbed. Amiloride Hydrochloride Tablets, USP usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and plasma half-life varies from 6 to 9 hours.

Amiloride hydrochloride is not metabolized by the liver. About 50% of a 20 mg dose of Amiloride Hydrochloride Tablets, USP is excreted unchanged in the urine and 40% is excreted in the stool within 72 hours. In clinical studies Amiloride Hydrochloride Tablets, USP was found to have little effect on glomerular filtration rate or renal blood flow.

INDICATIONS AND CLINICAL USE

Amiloride Hydrochloride Tablets, USP is indicated for use alone or concomitantly with thiazide diuretics or other kaliuretic-diuretic agents in the treatment of patients with cirrhosis of the liver with ascites and edema.

Amiloride Hydrochloride Tablets, USP is indicated as an adjunct to the treatment with thiazide diuretics or other kaliuretic-diuretic agents in those patients with edema of cardiac origin or hypertension who:

a) have hypokalemia, or
b) in whom maintenance of normal serum potassium levels is considered to be clinically important, e.g., digitalized patients, patients in whom adequate dietary intake of potassium is not feasible or patients with cardiac arrhythmias.

Use in Hepatic Cirrhosis with Ascites and Edema

Amiloride Hydrochloride Tablets, USP used alone may provide satisfactory diuresis with diminished potassium loss and with a reduced risk of metabolic alkalosis. In resistant cases Amiloride Hydrochloride Tablets, USP may be used with kaliuretic-

diuretic agents to help produce satisfactory diuresis, while maintaining a more balanced serum electrolyte pattern. As with all therapy for the ascites of hepatic cirrhosis, gradual weight loss and avoidance of electrolyte imbalance are the chief objectives (see PRECAUTIONS).

CONTRAINDICATIONS

Hyperkalemia

Amiloride Hydrochloride Tablets, USP should not be used in the presence of elevated serum potassium levels (see WARNINGS).

Antikaliuretic Therapy or Potassium Salts

Other antikaliuretic agents and potassium supplements are contraindicated in patients receiving amiloride hydrochloride (such combination therapy is commonly associated with rapid increases in plasma potassium levels).

Impaired Renal Function

Anuria, acute renal failure, severe or progressive renal disease, and diabetic nephropathy are contraindications to the use of Amiloride Hydrochloride Tablets, USP (see WARNINGS).

Hypersensitivity

Amiloride Hydrochloride Tablets, USP is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Hyperkalemia

Hyperkalemia (i.e., serum potassium levels over 5.5 mEq/L), has been observed in patients who received Amiloride Hydrochloride Tablets, USP either alone or with diuretics. This has been noted particularly in elderly patients, in diabetic patients, and in hospitalized patients with hepatic cirrhosis or cardiac edema who had known

renal impairment, were seriously ill, or were receiving vigorous diuretic therapy. Since fatalities have occurred, patients should be monitored carefully for clinical, laboratory, and electrocardiographic (ECG) evidence of hyperkalemia and for acidosis. Monitoring of the serum potassium level is important because hyperkalemia is not always associated with an abnormal ECG.

Warning signs or symptoms of hyperkalemia include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock, and ECG abnormalities.

When abnormal, the ECG in hyperkalemia is characterized primarily by tall, peaked T waves or elevations from previous tracings. There may also be lowering of the R wave and increased depth of the S wave, widening and even disappearance of the P wave, progressive widening of the QRS complex, prolongation of the PR interval, and ST depression.

If hyperkalemia occurs in patients taking Amiloride Hydrochloride Tablets, USP, the drug should be discontinued immediately. If the serum potassium level exceeds 6.5 mEq per liter, active measures should be taken to reduce it. Such measures include the intravenous administration of sodium bicarbonate solution or oral or parenteral glucose with a rapid-acting insulin preparation. If needed, a cation exchange resin such as sodium polystyrene sulfonate may be given orally or by enema. Patients with persistent hyperkalemia may require dialysis.

Diabetes Mellitus

In diabetic patients, hyperkalemia has been commonly reported with the use of Amiloride Hydrochloride Tablets, USP, particularly if they have chronic renal disease or prerenal azotemia. Some deaths occurred in this last group of patients. Therefore, if therapy with Amiloride Hydrochloride Tablets, USP is considered essential, the drug should be used with caution in diabetic or suspected diabetic patients and only after first determining the status of renal function.

Careful monitoring of serum potassium levels is required throughout the therapy.

One patient with poorly controlled diabetes mellitus who became severely hyperkalemic while on amiloride hydrochloride died following two repeated intravenous glucose tolerance tests. Therefore, Amiloride Hydrochloride Tablets, USP should be discontinued at least 3 days before glucose tolerance testing.

Metabolic or Respiratory Acidosis

Antikaliuretic therapy should be instituted only with caution in patients in whom respiratory or metabolic acidosis may occur, such as patients with cardiopulmonary disease or diabetes. If Amiloride Hydrochloride Tablets, USP is given to these patients, frequent monitoring of acid-base balance is necessary. Shifts in acid-base balance alter the ratio of extracellular/intracellular potassium, and the development of acidosis may be associated with rapid increases in serum potassium levels.

Impaired Renal Function

Patients with impaired renal function other than those listed under CONTRAINDICATIONS and who have BUN levels over 30 mg per 100 mL, serum creatinine levels over 1.5 mg per 100 mL, or with whole blood urea values over 60 mg per 100 mL or with diabetes mellitus, should not receive the drug without careful, frequent monitoring of serum electrolytes, creatinine, and BUN levels. Potassium retention associated with the use of Amiloride Hydrochloride Tablets, USP is accentuated in the presence of renal impairment and may result in the rapid development of hyperkalemia. Prolongation of amiloride hydrochloride excretion was observed in patients with renal impairment.

PRECAUTIONS

Electrolyte Imbalance and BUN Increases

Hyponatremia and hypochloremia may occur Amiloride Hydrochloride Tablets, USP is used with other diuretics. Increases in BUN levels have been reported. These increases usually have accompanied vigorous fluid elimination, especially when

diuretic therapy was used in seriously ill patients, such as those who had hepatic cirrhosis with ascites and metabolic alkalosis, or those with resistant edema. Therefore, careful monitoring of serum electrolytes and BUN levels is important when using Amiloride Hydrochloride Tablets, USP.

Effects Related to Diuresis in Cirrhotic Patients

Patients with hepatic cirrhosis and ascites are intolerant of acute shifts in electrolyte balance and often have pre-existing hypokalemia as a result of associated secondary hyperaldosteronism. When oral diuretic therapy is used, these patients should be carefully monitored and diuresis should be gradual.

Hepatic encephalopathy, manifested by tremors, confusion, and coma, has been reported in association with amiloride hydrochloride therapy.

In a few cirrhotic patients, pre-existing jaundice increased, but the relationship to drug is uncertain.

Use in Obstetrics

Teratologic studies with amiloride hydrochloride in rabbits and mice revealed no evidence of harm to the fetus. Reproduction studies in rats showed no evidence of impaired fertility. At approximately 5 or more times the expected maximum daily dose for humans, some toxicity was seen in adult rats and rabbits and a decrease in rat pup growth and survival occurred.

In rats a trace of drug crossed the placental barrier.

Because clinical experience is limited,Amiloride Hydrochloride Tablets, USP is not recommended for use during pregnancy. The potential benefits of the drug must be weighed against possible hazards to the fetus if it is administered to a woman of childbearing age.

Nursing Mothers

It is not known whether Amiloride Hydrochloride Tablets, USP is excreted in human milk. In rats secretion of amiloride hydrochloride in milk has been demonstrated. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use

The use of amiloride hydrochloride in children has not been established; therefore Amiloride Hydrochloride Tablets, USP is not recommended in the pediatric age group.

Drug Interactions

Lithium should generally not be given with diuretics because they reduce the renal clearance of lithium and add a high risk of lithium toxicity.

When amiloride HCl is administered concomitantly with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor antagonist, cyclosporine or tacrolimus, the risk of hyperkalemia may be increased. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing agents, including amiloride hydrochloride, may cause hyperkalemia and renal failure, particularly in elderly patients. Therefore, when amiloride hydrochloride is used concomitantly with NSAIDs, renal function and serum potassium levels should be carefully monitored.

ADVERSE REACTIONS

While rare, the most serious adverse effect of Amiloride Hydrochloride Tablets, USP is symptomatic hyperkalemia (symptoms of hyperkalemia may include paresthesias, muscular weakness, fatigue, flaccid paralysis of the extremities, bradycardia, shock and ECG abnormalities) (see CONTRAINDICATIONS and WARNINGS).

The following incidence of adverse reactions was determined from clinical trials (837 patients treated with Amiloride Hydrochloride Tablets, USP).

	Incidence ≥3%	Incidence >1%-<3%	Incidence ≤1%
Gastrointestinal (In 12.1% of patients)	Nausea/anorexia (6.1%) Diarrhea (3.8%) Vomiting (3.3%)	Abdominal pain Gas pain Appetite changes Constipation	Jaundice GI bleeding Abdominal fullness GI disturbance Thirst Heartburn Flatulence Dyspepsia Dryness of the mouth
Central Nervous System (In 9.6% of patients)	Headache (7.6%)	Dizziness Encephalopathy	Paresthesia Tremors Vertigo Nervousness Mental confusion Insomnia Decreased libido Depression Somnolence
Metabolic (In 8.0% of patients)	Asymptomatic hyperkalemia (8.0%)		Symptomatic hyperkalemia Hyponatremia
Musculoskeletal (In 6.1% of patients)		Muscle cramps Weakness Fatigability	Joint pain Leg ache Back pain Chest pain Neck/shoulder ache Pain extremities
Respiratory (In 2.0% of patients)		Cough Dyspnea	Shortness of breath
Urogenital (In 3.8% of patients)		Impotence	Polyuria Dysuria Urinary frequency Bladder spasms
Cardiovascular (In 1.5% of patients)			Angina pectoris Orthostatic hypotension Arrhythmia Palpitation One patient with a partial heart block developed complete heart block
Dermatologic (In 1.9% of patients)			Skin rash Pruritus Alopecia
Special Senses (In 2.9% of patients)			Visual disturbances Nasal congestion Increased intraocular pressure Tinnitus

Causal Relationship Unknown

A causal relationship could not be established with other reactions reported rarely. However, the possibility could not be excluded. These reactions were:

Activation of probable pre-existing peptic ulcer
Aplastic anemia
Neutropenia
Abnormalities of liver function tests

In cirrhotic patients, jaundice associated with the underlying disease process has deepened in a few instances, but the relationship to drug is uncertain.

In patients with pre-existing severe liver disease, hepatic encephalopathy, manifested by tremors, confusion, and coma, and increased jaundice, have been reported in association with diuretics, including amiloride hydrochloride.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data are available in regard to overdosage in humans.

It is not known whether the drug is dialyzable.

If hyperkalemia occurs, active measures should be taken to reduce the serum potassium levels (see WARNINGS).

The most likely signs and symptoms to be expected with overdosage are dehydration and electrolyte imbalance. These can be treated by established procedures. Therapy with Amiloride Hydrochloride Tablets, USP should be discontinued and the patient observed closely. There is no specific antidote. Emesis should be induced or gastric lavage performed. Treatment is symptomatic and supportive.

DOSAGE AND ADMINISTRATION

The incidence of hyperkalemia is dose-related and this should be considered especially when daily doses over 10 mg are used.

Hepatic cirrhosis with ascites and edema

Treatment should be started with a small dose of Amiloride Hydrochloride Tablets, USP i.e., one 5 mg tablet daily, plus a small dose of a diuretic agent (other than antikaliuretics). If necessary, dosages of both drugs may be increased gradually until effective diuresis is obtained. The dosage of Amiloride Hydrochloride Tablets, USP should not exceed four tablets (20 mg) a day. Maintenance doses may be lower than those required to initiate diuresis; therefore, reduction in the daily dosage should be attempted when the patient's weight is stabilized. In cirrhotic patients, gradual weight reduction is especially desirable to reduce the likelihood of untoward reactions associated with diuretic therapy.

In those instances where Amiloride Hydrochloride Tablets, USP is used alone, the initial daily dosage should be two 5 mg tablets (as a single dose or one tablet twice a day). Dosage may be increased depending on the need. The total daily dosage should not exceed four tablets (20 mg). After diuresis has been achieved the dosage may be reduced by decrements of one tablet to the least amount required.

Edema of cardiac origin

Amiloride Hydrochloride Tablets, USP, one or two 5 mg tablets daily, may be given with the usual doses of a diuretic agent (other than antikaliuretics). This dose is sufficient in most cases. If potassium levels remain low the dosage of Amiloride Hydrochloride Tablets, USP may be increased gradually. The dosage of Amiloride Hydrochloride Tablets, USP should not exceed four tablets (20 mg) a day.

The optimal dosage is determined by the serum potassium level. Reduction in dosage should be attempted for maintenance therapy. Maintenance therapy may be on an intermittent basis.

Hypertension

Amiloride Hydrochloride Tablets, USP, one or two 5 mg tablets daily, is given with the usual antihypertensive dosage of a diuretic agent (other than antikaliuretics). The dosage may be adjusted if necessary. More than two 5 mg tablets of Amiloride Hydrochloride Tablets, USPdaily usually is not needed; in any event, the maximum dosage is four tablets (20 mg) a day.

PHARMACEUTICAL INFORMATION

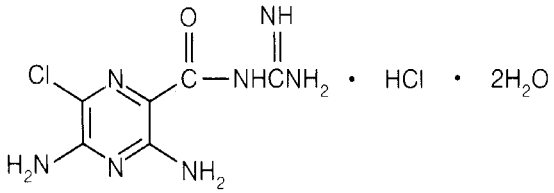
I. DRUG SUBSTANCE

Proper name: amiloride hydrochloride

Chemical Name: 3,5-diamino-*N*-(aminoiminomethyl)-6-chloropyrazinecarboxamide monohydrochloride, dihydrate.

Molecular Formula: $C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$

Structural Formula:



Molecular Weight: 302.12

Description: A yellow to greenish yellow, odourless or practically odourless, crystalline compound, soluble in water.

II. COMPOSITION

Each tablet contains 5 mg of amiloride hydrochloride and the following non-medicinal ingredients:

calcium phosphate dibasic
corn starch
lactose
magnesium stearate

Amiloride Hydrochloride Tablets, USP, 5 mg also contain D&C Yellow No. 10 and Red Ferric Oxide.

AVAILABILITY

Amiloride Hydrochloride Tablets, USP, 5 mg tablets, are yellow, diamond-shaped, compressed tablets, coded MSD 92 on one side and MIDAMOR on the other. They are supplied in bottles of 100 tablets.

PHARMACOLOGY

Amiloride hydrochloride is chemically unrelated to other known antikaliuretic or diuretic agents. It is a salt of a moderately strong base (pKa 8.7).

In rats and dogs, amiloride hydrochloride in an oral dose of 0.1 mg/kg or less increases the excretion of sodium and, to a lesser extent, of chloride but does not increase the excretion of potassium.

A potassium-retaining effect is seen in experimental animals, especially under conditions of high potassium excretion, as upon loading with potassium chloride, after pretreatment with acetazolamide or thiazides, or in deoxycorticosterone-treated

adrenalectomized rats. The natriuresis is accompanied by an increase in urinary pH, reflecting a decrease in hydrogen ion excretion.

Following oral administration to dogs, amiloride hydrochloride increases the rate of sodium excretion less than do the more potent agents, but the moderate effect on sodium excretion has an extended duration. Natriuresis increases only moderately as the oral dose is increased from 0.25 to 4.0 mg/kg, this activity persists beyond 6 hours.

An increase in sodium excretion is produced when amiloride hydrochloride is given together with chlorothiazide, hydrochlorothiazide, or acetazolamide in rats. Amiloride hydrochloride antagonizes the kaliuretic effect of the other diuretic. Oral doses of amiloride hydrochloride (0.1 to 0.5 mg/kg) increase the excretion of sodium and decrease that of potassium in dogs given ethacrynic acid (1.0 mg/kg) or hydrochlorothiazide (0.5 mg/kg) orally.

Amiloride hydrochloride increases the Na^+/K^+ excretion ratio in adrenalectomized rats. In adrenalectomized rats treated with aldosterone, deoxycorticosterone, or hydrocortisone, amiloride hydrochloride not only reverses the steroid-induced sodium retention, but increases the Na^+/K^+ excretion ratio substantially above that of untreated adrenalectomized rats.

Stop-flow studies in dogs indicate that amiloride hydrochloride inhibits tubular secretion of potassium and reabsorption of sodium in the distal portion of the nephron. In renal clearance studies, 1.0 mg/kg intravenously did not affect glomerular filtration rate, effective renal plasma flow, or glucose reabsorption. An enzymatic basis for the renal action of amiloride hydrochloride has not been elucidated. It is not an inhibitor of carbonic anhydrase.

Amiloride hydrochloride given parenterally (2.5 to 5.0 mg/kg) to anesthetized dogs produces profound reduction of blood pressure and produces changes in the electrocardiogram. The effects which are coincident with the release of histamine

into plasma, are not seen if the compound is injected slowly or if lower doses are given. A slight increase in gastric secretion and intestinal motility occurred after oral administration to dogs of 0.5 to 2.0 mg/kg. Pretreatment for several days with amiloride hydrochloride in a dose of 5 mg/kg/day by mouth does not alter the response of dogs to ouabain.

TOXICOLOGY

Acute Toxicity (LD_{50})

Species	Sex	Route	LD_{50}
Albino Mice CF_1S Strain	F	Oral	56 mg/kg[a]
Albino Mice CF_1S Strain	F	IV	24.5 mg/kg[a]
Rat (Adult) Charles River CD Strain	M & F	Oral IV	84.5 mg/kg[a] 38.9 mg/kg[a]
Rat (Young Adult) Camm Strain	M F	Oral Oral	36 mg/kg[b] 41 mg/kg[b]
Rat (Weanling) Camm Strain	M F	Oral Oral	54 mg/kg[b] 59 mg/kg[b]
Rat (Infant) Camm Strain	M & F	Oral	*

[a] = 14-day mortality response
[b] = 5-day mortality response
* The extreme variability of responses in the infant rats did not permit the estimation of a reproducible LD_{50} value.

Major signs of toxicity were ataxia, bradypnea, tremors and loss of righting reflex.

Subacute and Chronic Toxicity

MODERATE TO MARKED HYPERKALEMIA DEVELOPED AT DOSES GREATER THAN 8.0 mg/kg/day. ELECTROCARDIOGRAPHIC CHANGES WERE OBSERVED. SERUM SODIUM AND CHLORIDE DECREASED.

Rats were administered 0, 2.5, 5, 10 or 20 mg/kg/day of amiloride for 5 weeks by the oral route. The lower doses showed mild toxicity; gastric lesions, similar to stress ulcers, were observed at 10 and 20 mg/kg/day.

Superficial ulceration of the stomach or intestine was seen in 2 of 12 dogs in a 6 week oral study.

Rats received amiloride hydrochloride by oral route at doses of 0, 2.5, 5.0 and 10 to 15 mg/kg for up to 80 weeks. Inhibition of weight gain occurred in male rats. Treatment related changes included alterations in urinary and serum sodium and potassium, renal tubular dilatation and a dose-dependent hyperplasia of the adrenal zona glomerulosa. Hypotonia of muscles, loss of righting reflex and coma occurred in moribund rats (high dose group). Symptoms of electrolyte imbalance including paraphimosis, occurred at doses of 10 mg/kg/day during a one year study.

Dogs treated with oral doses of 0, 2, 4 and 8 mg/kg/day (base) for one year showed changes in body weight, water intake and serum electrolytes. Positive fecal occult blood occurred at a slightly greater incidence in treated animals but no evidence of gastrointestinal ulceration was seen. Doses producing marked electrolyte changes had no effect on blood glucose or glucose tolerance. Dose-dependent hyperplasia of the zona glomerulosa of the adrenals was observed in all treated dogs.

In monkeys treated with oral doses of 0, 2, 4 and 8 (increased to 15.8) mg/kg/day for one year, excitable and irritable behavior occurred at the highest dose. Increase in serum potassium and decrease in serum sodium occurred at doses as low as 4 mg/kg/day. Although adrenal glands of some high and middle dose animals appeared enlarged, hyperplasia of the zona glomerulosa was not observed. Urinary excretion of aldosterone was increased in high dose animals.

Special Studies Relative to Adrenal Zona Glomerulosa, Hyperplasia and Diabetes

Amiloride hydrochloride produced a dose-dependent hyperplasia of the zona glomerulosa of the adrenal cortex in rats and dogs and to a lesser extent in monkeys. In rats reversibility of the hyperplasia was demonstrated after the drug was given for 58 weeks and the animals were observed for an additional 22 weeks. Hyperplasia has been shown to disappear in 19 to 30 days after cessation of treatment and the adrenals were normal within 30 to 58 days. The hyperplasia can be reduced by substitution of physiologic saline for drinking water. Hyperplasia of the adrenal zona glomerulosa occurred in maternal mice but not in the offspring in a teratogenic study. The hyperplasia is considered to be induced by alteration of serum electrolytes and/or inhibition of aldosterone activity.

No effect on carbohydrate metabolism was observed when the toxicity of amiloride hydrochloride was studied in obese diabetic Zucker rats and normal-thin rats. Amiloride hydrochloride had no adverse effect on glucose tolerance in acute experiments in rats or a chronic study in dogs.

The effect of amiloride hydrochloride on I^{131} uptake was measured in immature female rats. A dose of about 5 or 10 mg/kg/day given subcutaneously every 8 hours for 21 days did not alter I^{131} uptake.

Teratogenic and Reproduction Studies

Amiloride hydrochloride had no teratogenic effect by external, visceral, or skeletal examination of the progeny of albino New Zealand rabbits treated orally with 2, 4, or 8 mg/kg/day (base) on days 6 through 18 of gestation or CF_1 albino mice treated orally with 2.5, 5.0 or 10.0 mg/kg/day (base) on days 6 through 15 of gestation. In rabbits the highest dose caused definite maternal weight loss; in mice 10 mg/kg/day was toxic (6 of 19 died).

No effect on reproductive performance or fertility in albino rats (COBS strain) given 2, 4 or 8 mg/kg/day (base) orally was noted. Growth rate and food consumption

were reduced at the highest dose. Doses of 4 and 8 mg/kg/day were administered without effect during late gestation and growth. The high dose adversely affected pup survival and growth.

Carcinogenic and Mutagenic Studies (Charles River - CD strains)

Amiloride hydrochloride had no apparent carcinogenic effect in albino mice treated with oral doses up to 10 mg/kg/day for 92 weeks or in rats treated with oral doses up to 8 mg/kg/day for 104 weeks. These strains of rats and mice have been shown to be susceptible to the activity of a known carcinogen.

Amiloride hydrochloride did not have any mutagenic activity in the Ames microbial mutagen assay with or without rat liver activation systems.

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